Complete Summary

GUIDELINE TITLE

Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review). Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, Jankovic J, Karp B, Ludlow CL, Miyasaki JM, Naumann M, So Y, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008 May 6;70(19):1699-706. [35 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Movement disorders:

- Blepharospasm
- Hemifacial spasm
- Cervical dystonia (CD)
- Focal limb dystonia
- Laryngeal dystonia

- Tics (e.g., motor, phonic)
- Tremor

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Technology Assessment
Treatment

CLINICAL SPECIALTY

Neurology
Otolaryngology
Pharmacology
Physical Medicine and Rehabilitation

INTENDED USERS

Pharmacists
Physicians

GUIDELINE OBJECTIVE(S)

- To perform an evidence-based review of the safety and efficacy of botulinum neurotoxin (BoNT) in the treatment of movement disorders
- To make evidence-based recommendations

TARGET POPULATION

Adult patients with movement disorders

INTERVENTIONS AND PRACTICES CONSIDERED

Botulinum neurotoxin (BoNT) injection

MAJOR OUTCOMES CONSIDERED

- Functional improvement
    - Patient subjective rating
    - Physician assessment
    - Videotape rating
    - Fahn scale rating
    - TWSTRS score
    - Tsui score
    - Handwriting accuracy/speed
    - Quantitative measures of voice function
    - Tic frequency and urge scores
    - Global disability
    - Tremor severity rating
    - Sickness Impact Profile (SIP)
- Duration of action

- Adverse events

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The literature search used MEDLINE and Current Contents for relevant, fully published, peer-reviewed articles up to April 2007 and was supplemented through manual searches by panel members. The search terms used were botulinum toxin and movement disorders, dystonia, tics, tremors, hemifacial spasm, blepharospasm, cerebral palsy, spasticity, autonomic, Frey's syndrome, sweating, hyperhidrosis, drooling, headache, back pain, pain, laryngeal disorders, dysphonia, and urologic disorders. The following criteria were used: 1) relevant to the clinical questions of efficacy, safety, tolerability, or mode of use; 2) limited to human subjects; 3) limited to therapeutic studies. Abstracts, reviews, and meta-analyses were excluded.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Classification of Evidence for Therapeutic Intervention

Class I: Randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: a) concealed allocation, b) primary outcome(s) clearly defined, c) exclusion/inclusion criteria clearly defined, and d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a randomized controlled trial in a representative population that lacks one criteria a-d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where

outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

*Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The panel was comprised of specialists with experience in the therapeutic use of botulinum neurotoxin (BoNT) for the indications under consideration or with expertise in guideline methodology. Each article was reviewed by at least two panelists who did not participate in the trial reported. The articles were classified as Class I through IV using the American Association of Neurology (AAN) guideline process (see "Rating Scheme for the Strength of the Evidence"). Disagreements on article classification were resolved by discussion and consensus.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Conclusions and recommendations were made according to the American Academy of Neurology (AAN) criteria for translating the quality of evidence for therapeutic interventions into recommendations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Classification of Recommendations

The strength of practice recommendations is linked directly to the level of evidence:

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I–Class III).

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met and/or 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines were reviewed for accuracy, quality, and thoroughness by the American Academy of Neurology members, topic experts, and pertinent physician organizations.

The guideline was approved by the Therapeutics and Technology Assessment Subcommittee on March 31, 2007; by the Practice Committee on July 12, 2007; and by the American Academy of Neurology (AAN) Board of Directors on January 30, 2008.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the levels of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Blepharospasm

Conclusions

For patients with blepharospasm, botulinum neurotoxin (BoNT) injection is probably effective with minimal side effects (**two Class II studies**). After dosage adjustment, Botox® and Xeomin® are probably equivalent (**one Class I study**), and Botox® and Dysport® are possibly equivalent (**one Class II and one Class III study**).

Recommendation

BoNT injection should be considered as a treatment option for blepharospasm (**Level B**).

Hemifacial Spasm

Conclusions

BoNT is possibly effective with minimal side effects for the treatment of hemifacial spasm (**one Class II and one Class III study**). Botox® and Dysport®, after dosage adjustment, are possibly equivalent in efficacy (**one Class II study**).

Recommendation

BoNT injection may be considered as a treatment option for hemifacial spasm (**Level C**).

Cervical Dystonia

Conclusion

BoNT is established as safe and effective for the treatment of CD (**seven Class I studies**).

Recommendations

- BoNT injection should be offered as a treatment option to patients with cervical dystonia (**Level A**).
- BoNT is probably more efficacious and better tolerated in patients with CD than treatment with trihexyphenidyl (**Level B**).

Focal Limb Dystonia

Conclusions

BoNT is probably effective for the treatment of focal upper extremity limb dystonia (**one Class I and three Class II studies**). While a few patients in one Class II study suggest that BoNT may be effective for lower extremity dystonia, the data are inadequate to provide a recommendation.

Recommendation

BoNT should be considered as a treatment option for focal upper extremity dystonia (**Level B**).

Laryngeal Dystonia

Conclusions

BoNT is probably effective for the treatment of adductor type spasmodic dysphonia (ADSD) (**one Class I study**). There is insufficient evidence to support

a conclusion of effectiveness for BoNT in abductor type spasmodic dysphonia (ABSD).

Recommendations

- BoNT should be considered as a treatment option for adductor spasmodic dysphonia (**Level B**).
- There is insufficient evidence to support or refute the use of BoNT in abductor spasmodic dysphonia (**Level U**).

Tics

Conclusions

BoNT is possibly effective for the treatment of motor tics (**one Class II study**). There are insufficient data to determine the effectiveness of BoNT in phonic tics (**one Class IV study**).

Recommendation

BoNT may be considered as a treatment option for motor tics (**Level C**).

Tremor

Conclusions

BoNT injection of forearm muscles is probably effective in reducing the tremor amplitude in patients with essential hand tremor (**two Class II studies**). The benefits must be considered in conjunction with the common adverse effect of muscle weakness associated with BoNT injection. Existing data are insufficient to draw a conclusion on the use of BoNT in the treatment of head and voice tremor.

Recommendation

BoNT should be considered as a treatment option for essential hand tremor in those patients who fail treatment with oral agents (**Level B**).

Definitions:

Classification of Recommendations

Level A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.*)

Level B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or at least two consistent Class II studies.)

Level C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies)

Level U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven. (Studies not meeting criteria for Class I–Class III).

* In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met and/or 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2.

Classification of Evidence for Therapeutic Intervention

Class I: Randomized, controlled clinical trial with masked or objective outcome assessment in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are required: a) concealed allocation, b) primary outcome(s) clearly defined, c) exclusion/inclusion criteria clearly defined, and d) adequate accounting for drop-outs (with at least 80% of enrolled subjects completing the study) and cross-overs with numbers sufficiently low to have minimal potential for bias.

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets b-d above OR a randomized controlled trial in a representative population that lacks one criteria a-d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.*

Class IV: Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

*Objective outcome measurement: An outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of botulinum neurotoxin (BoNT) for treatment of movement disorders in adults

POTENTIAL HARMS

- Undesirable effects associated with administration of botulinum neurotoxin (BoNT) fall into three broad categories. First, diffusion of the toxin from the intended sites of action can lead to unwanted inhibition of transmission at neighboring nerve endings. Second, sustained blockade of transmission can produce effects similar to anatomical denervation, including muscle atrophy. The third undesirable effect is immunoresistance to BoNT.
- Adverse events reported for BoNT in the treatment of movement disorders include:
    - Dry eye
    - Tearing
    - Ptosis
    - Diplopia
    - Lid edema
    - Ecchymosis
    - Weakness/neck weakness/focal weakness
    - Pain
    - Dysphagia
    - Dry mouth
    - Breathiness
    - Bleeding
    - Bruising

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This statement is provided as an educational service of the American Academy of Neurology (AAN). It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved. The clinical context section is made available in order to place the evidence-based guideline(s) into perspective with current practice habits and challenges. No formal practice recommendations should be inferred.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Quick Reference Guides/Physician Guides
Slide Presentation
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Simpson DM, Blitzer A, Brashear A, Comella C, Dubinsky R, Hallett M, Jankovic J, Karp B, Ludlow CL, Miyasaki JM, Naumann M, So Y, Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008 May 6;70(19):1699-706. [35 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 May 6

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Therapeutics and Technology Assessment Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: D.M. Simpson, MD; A. Blitzer, MD, DDS; A. Brashear, MD; C. Comella, MD; R. Dubinsky, MD, MPH; M. Hallett, MD; J. Jankovic, MD; B. Karp, MD; C.L. Ludlow, PhD; J.M. Miyasaki, MD, MEd; M. Naumann, MD; Y. So, MD, PhD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guidelines have been reviewed by at least three AAN committees, a network of neurologists, *Neurology*® peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com.

The authors report the following conflicts: Dr. Simpson has received speaker honoraria and research support from Allergan, Merz, and Solstice, Inc., and performs botulinum toxin injections. Dr. Blitzer has received speaker honoraria from Allergan, Solstice, and Merz; research support from Allergan; and performs botulinum toxin injections. Dr. Brashear has received speaker honoraria from Allergan, Solstice, and Merz; research support from Allergan, Ipsen, Merz, and Oviation; performs botulinum toxin injections and has received payment for expert testimony. Dr. Comella has received speaker honoraria from Jazz Pharmaceutical, Merz Pharmaceutical, and UCB Pharmaceutical; research support from Allergan, Dystonia Study Group, and Solstice; and performs botulinum toxin injections. Dr. Dubinsky has received speaker honoraria from Allergan and research support from Allergan, MERZ-INC, and Solstice Neurosciences. Dr. Dubinsky holds financial interest in Abbott Laboratories (spouse), performs botulinum toxin injections, and presents annual courses at AANEM on chemodenervation. Dr. Hallett holds financial interest in Amylin Pharmaceuticals, Eli Lilly, Genetech, Genzyme, Healthsouth Corp., Medtronic, Pfizer, St. Jude Medical, Triad Hospitals, United Healthcare, and Valeant Pharmaceuticals International and performs botulinum toxin injections. Dr. Jankovic has received speaker honoraria from Allergan and Merz Pharmaceutical, research support from Allergan, Ipsen, and Merz Pharmaceutical, and performs botulinum toxin injections. Dr. Karp performs botulinum toxin injections. Dr. Ludlow holds financial interest in Fidelity Biotechnology (family member). Dr. Miyasaki has received

research support from Boehringer Ingelheim, Huntington Study Group, NIH, Solvay, Solstice, and Teva. Dr. Naumann has received speaker honoraria from Ipsen and Allergan and performs botulinum toxin injections. Dr. So holds financial interest in Satoris Inc., and has received research support from NIH, Pfizer, Inc., and NeurogesX, Inc.

ENDORSER(S)

American Academy of Physical Medicine and Rehabilitation - Medical Specialty Society

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Use of botulinum neurotoxin for the treatment of movement disorders. AAN summary of evidence-based guidelines for clinicians. St. Paul (MN): American Academy of Neurology. 2008. 2 p. Available in Portable Document Format (PDF) from the AAN Web site.
- Assessment: botulinum neurotoxin for the treatment of autonomic disorders and pain, movement disorders, and spasticity (an evidence-based review). Slide presentation. St. Paul (MN): American Academy of Neurology. 2008. 146 p. Available from the AAN Web site.
- Assessment: botulinum neurotoxin for the treatment of autonomic disorders and pain, movement disorders, and spasticity (an evidence-based review). Case study and coding. St. Paul (MN): American Academy of Neurology. 2008. 3 p. Available from the AAN Web site.
- Assessment: botulinum neurotoxin for the treatment of autonomic disorders and pain, movement disorders, and spasticity (an evidence-based review). Case study in *Neurology Today*®. St. Paul (MN): American Academy of Neurology. 2008. 1 p. Available from the AAN Web site.
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Available from the AAN Web site.

PATIENT RESOURCES

The following is available:

- Use of botulinum neurotoxin injections to treat movement disorders. AAN summary of evidence-based guideline for patients and their families. St. Paul (MN): American Academy of Neurology (AAN). 2008. 2 p.

Electronic copies: Available in Portable Document Format (PDF) from the AAN Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI Institute on November 3, 2008. The information was verified by the guideline developer on December 30, 2008.

COPYRIGHT STATEMENT

DISCLAIMER

NGC DISCLAIMER

The National Guideline Clearinghouse™ (NGC) does not develop, produce, approve, or endorse the guidelines represented on this site.

All guidelines summarized by NGC and hosted on our site are produced under the auspices of medical specialty societies, relevant professional associations, public or private organizations, other government agencies, health care organizations or plans, and similar entities.

Guidelines represented on the NGC Web site are submitted by guideline developers, and are screened solely to determine that they meet the NGC Inclusion Criteria which may be found at http://www.guideline.gov/about/inclusion.aspx .

NGC, AHRQ, and its contractor ECRI Institute make no warranties concerning the content or clinical efficacy or effectiveness of the clinical practice guidelines and related materials represented on this site. Moreover, the views and opinions of developers or authors of guidelines represented on this site do not necessarily state or reflect those of NGC, AHRQ, or its contractor ECRI Institute, and inclusion or hosting of guidelines in NGC may not be used for advertising or commercial endorsement purposes.

Readers with questions regarding guideline content are directed to contact the guideline developer.

Date Modified: 1/26/2009